

Released May 26, 2009

This e-newsletter presents reviews of important, recently published scientific articles selected by The North American Menopause Society (NAMS), the leading nonprofit scientific organization dedicated to improving women's health and quality of life through an understanding of menopause. Each has a commentary from a recognized expert that addresses the clinical relevance of the item. Oversight for this e-newsletter issue was by Peter F. Schnatz, DO, Chair-Elect, 2008-2009 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Schnatz. Disclosures are available on request. Past issues of this e-newsletter may be viewed on the NAMS Web site (www.menopause.org/news.html).

Exercise-induced quality of life

Martin CK, Church TS, Thompson AM, Earnest CP, Blair SN. Exercise dose and quality of life: a randomized controlled trial. *Arch Intern Med* 2009;169:269-278.

Level of evidence: I.

Abstract copyright © 2009 American Medical Association. All rights reserved. Used with permission.

BACKGROUND: Improved quality of life (QOL) is a purported benefit of exercise, but few randomized controlled trials and no dose-response trials have been conducted to examine this assertion. **METHODS:** The effect of 50%, 100%, and 150% of the physical activity recommendation on QOL was examined in a 6-month randomized controlled trial. Participants were 430 sedentary postmenopausal women (body mass index range, 25.0-43.0 [calculated as weight in kilograms divided by height in meters squared]) with elevated systolic blood pressure randomized to a nonexercise control group (n = 92) or 1 of 3 exercise groups: exercise energy expenditure of 4 (n = 147), 8 (n = 96), or 12 (n = 95) kilocalories per kilogram of body weight per week. Eight aspects of physical and mental QOL were measured at baseline and month 6 with the use of the Medical Outcomes Study 36-Item Short Form Health Survey. **RESULTS:** Change in all mental and physical aspects of QOL, except bodily pain, was dose dependent (trend analyses were significant, and exercise dose was a significant predictor of QOL change; $P < .05$).

Higher doses of exercise were associated with larger improvements in mental and physical aspects of QOL. Controlling for weight change did not attenuate the exercise-QOL association. **CONCLUSION:** Exercise-induced QOL improvements were dose dependent and independent of weight change.

Comment. Exercise is reputed to be associated with health benefits in many studies. But since the Women's Health Initiative, menopause clinicians are sensitive to the perils of accepting observational data as fact, as well as the complexity of the effects of intervention on the QOL of a study population. The ambitious undertaking reported in this study—a randomized controlled trial to prove exercise improves QOL in a dose-dependent manner—has satisfying results. Exercise makes women around the time of menopause feel better, even exercise in less than the amount generally recommended and even when they don't lose weight. This study supports the notion that we can and should continue to recommend exercise for our patients and "treat physical activity as a legitimate medical therapy—even though it does not come in a pill," as Timothy S. Church, MD, proposes in an editorial in the *British Journal of Sports Medicine*.¹

However, many questions remain about exercise and its importance and relevance in the therapeutic armamentarium of healthcare

providers. Most compelling is how to get our patients to embark on an exercise regimen without paying them \$500, as was done in this current study? And then, how can we ensure they continue their efforts beyond 6 months? Martin et al suggest that some exercise is better than none—good news for our patients who insist they do not have time to exercise 30 minutes per day most days. Prescriptions for exercise should be dispensed aggressively by clinicians while researchers continue to help us sort out benefits, harms, and effective strategies for individualizing exercise plans and ensuring compliance with this QOL enhancer.

Marcie K. Richardson, MD, NCMP
 Director
 Harvard Vanguard Menopause Consultation Service
 Boston, MA
 Member, NAMS Consumer Education Committee
 NAMS Certified Menopause Practitioner

References:

1. Church TS, Blair SN. When will we treat physical activity as a legitimate medical therapy...even though it does not come in a pill? *Br J Sports Med* 2009;43:80-81.

Do macronutrients affect weight loss?

Sacks FM, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med* 2009;360:859-873. **Level of evidence: I.**

Abstract copyright © 2009 Massachusetts Medical Society. All rights reserved. Used with permission.

BACKGROUND: The possible advantage for weight loss of a diet that emphasizes protein, fat, or carbohydrates has not been established, and there are few studies that extend beyond 1 year. **METHODS:** We randomly assigned 811 overweight adults to one of four diets; the targeted percentages of energy derived from fat, protein, and carbohydrates in the four diets were 20, 15, and 65%; 20, 25, and 55%; 40, 15, and 45%; and 40, 25, and 35%. The diets consisted of similar foods and met guidelines for cardiovascular health. The participants were offered group and individual instructional sessions for 2 years. The primary outcome was

the change in body weight after 2 years in two-by-two factorial comparisons of low fat versus high fat and average protein versus high protein and in the comparison of highest and lowest carbohydrate content. **RESULTS:** At 6 months, participants assigned to each diet had lost an average of 6 kg, which represented 7% of their initial weight; they began to regain weight after 12 months. By 2 years, weight loss remained similar in those who were assigned to a diet with 15% protein and those assigned to a diet with 25% protein (3.0 and 3.6 kg, respectively); in those assigned to a diet with 20% fat and those assigned to a diet with 40% fat (3.3 kg for both groups); and in those assigned to a diet with 65% carbohydrates and those assigned to a diet with 35% carbohydrates (2.9 and 3.4 kg, respectively) ($P>0.20$ for all comparisons). Among the 80% of participants who completed the trial, the average weight loss was 4 kg; 14 to 15% of the participants had a reduction of at least 10% of their initial body weight. Satiety, hunger, satisfaction with the diet, and attendance at group sessions were similar for all diets; attendance was strongly associated with weight loss (0.2 kg per session attended). The diets improved lipid-related risk factors and fasting insulin levels. **CONCLUSIONS:** Reduced-calorie diets result in clinically meaningful weight loss regardless of which macronutrients they emphasize.

Comment. The primary conclusion of this study is that for weight loss, it's all about calories. The authors set out to determine if macronutrient intake emphasizing either fat, protein, or carbohydrates would affect overall weight loss. The study is unique in that a substantial number of subjects were recruited, recidivism was low, and participants were followed for 2 years (longer than many previous studies). Participants received extensive education and behavioral modification in the form of weekly individual and group sessions. Despite this counseling, it is notable that target goals for macronutrient intake were not reached, suggesting that sustained adherence to a specific macronutrient regimen is not feasible and, more important for

the purpose of weight loss, not necessary. Regardless of type of dietary intervention, participants reported a similar degree of fullness, hunger, and satisfaction with their diet—and had equivalent weight loss at 2 years. Other recent weight-loss studies have resulted in a lack of long-term benefit from a particular macronutrient composition¹ or for a particular popular dietary regimen.²

However, macronutrient composition was significant in the magnitude of cardiovascular risk reduction. All diets were associated with similar reductions in triglyceride and blood pressure. The high-protein diets were associated with the greatest reduction in insulin resistance, while higher-fat diets resulted in the most significant improvements in high-density lipoprotein levels. The effect on cardiovascular risk factors is best determined when weight is held constant, as modest weight loss itself will result in improvement of cardiovascular risk. The OmniHeart study³ did just that, showing that when comparing eucaloric diets, those predominant in protein and monounsaturated fat were superior to those predominant in carbohydrate (with an overall reduction in the Framingham risk score of 30%, a finding that correlates to the results of Sacks et al).

Finally, Sacks et al highlighted that adherence to behavioral modification is of primary importance in inducing weight loss. Subjects' attendance at behavioral support groups strongly predicted weight loss at 2 years and was similar among all diet groups, reminding us that when prescribing caloric restriction, it is not so much the macronutrient composition that is important but rather the implementation of behavioral and total lifestyle modification.

Adrienne Youdim, MD
 Director, Medical Weight Loss
 Cedars-Sinai Center for Weight Loss
 Assistant Clinical Professor
 UCLA School of Medicine
 Los Angeles, CA

References:

1. Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med* 2003;348:2082-2090.
2. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone Diets for weight loss and heart disease risk reduction. *JAMA* 2005;293:43-53.
3. Appel LJ, Sacks FM, Carey VJ, et al, for the OmniHeart Collaborative Research Group. Effect of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. *JAMA* 2005;294:2455-2464.

Depression and coronary heart disease

Whang W, Kubzansky LD, Kawachi I, et al. Depression and risk of sudden cardiac death and coronary heart disease in women: results from the Nurses' Health Study. *J Am Coll Cardiol* 2009;53:959-961. **Level of evidence: II-2**

Abstract copyright © 2009 Elsevier. All rights reserved. Used with permission.

OBJECTIVES: We assessed the association between depression and sudden cardiac death (SCD) and cardiac events among individuals without baseline coronary heart disease (CHD). **BACKGROUND:** Depression is a risk factor for cardiac events and mortality among those with CHD, possibly from arrhythmia. **METHODS:** We studied depressive symptoms and a proxy variable for clinical depression consisting of severe symptoms and/or antidepressant medication use and their relationship to cardiac events in the Nurses' Health Study. Questionnaires in 1992, 1996, and 2000 assessed symptoms with the Mental Health Index (MHI-5), and antidepressant use was assessed in 1996 and 2000. Primary end points included SCD, fatal CHD, and nonfatal myocardial infarction. **RESULTS:** Among 63,469 women without prior CHD/stroke in 1992, 7.9% had MHI-5 scores <53, previously found to predict clinical depression. Depressive symptoms were associated with CHD events, and the relationship was strongest for fatal

CHD, where the association remained significant even after controlling for CHD risk factors (hazard ratio [HR]: 1.49; 95% confidence interval [CI]: 1.11 to 2.00 for MHI-5 score <53). In models from 1996 onward, our proxy variable for clinical depression was most associated with SCD in multivariable models (HR: 2.33, 95% CI: 1.47 to 3.70), and this risk was primarily due to a specific relationship between antidepressant use and SCD (HR: 3.34, 95% CI: 2.03 to 5.50). **CONCLUSIONS:** In this cohort of women without baseline CHD, depressive symptoms were associated with fatal CHD, and a measure of clinical depression including antidepressant use was specifically associated with SCD. Although antidepressant use might be a marker of worse depression, its specific association with SCD merits further study.

Comment. This important paper adds to the growing literature on the link between depression and coronary heart disease (CHD). Whang et al analyzed the relationship between preexisting depression and risk of CHD outcomes in women without preexisting CHD. Of interest was the relationship between the symptoms of depression and other risk factors for CHD, including hypertension, diabetes, high cholesterol, smoking, obesity, and less exercise. Even when all these factors were taken into account in multivariate analysis, a significant relationship remained between depressive symptoms score and fatal CHD. Also of interest was the elevated risk of SCD associated with antidepressant use in the fully adjusted models. There was no relationship between antidepressant use and fatal CHD or nonfatal myocardial infarction (MI) in these models. There were similar hazard ratios for selective serotonin-reuptake inhibitor (SSRI) use compared with non-SSRIs.

An association between depression and poor prognosis after MI has been known for some time; the authors refer to a randomized trial,¹ which did not show increase or decrease in the risk of death or recurrent MI amongst post-MI patients treated with cognitive behavioral therapy and SSRIs. However, there were higher risks of

cardiovascular events among women treated with the intervention. Both SSRIs and tricyclic antidepressants are known to affect QT interval prolongation. This suggests that proarrhythmic effects from antidepressant medications might have resulted in a higher risk of SCD. Observational studies, however, cannot prove causality and confounding cannot be ruled out. For example, antidepressant use correlated more significantly with a diagnosis of clinical depression and it may be that those women with severe depression are more at risk for SCD. Other comorbid psychological factors such as anxiety may be responsible for arrhythmia.

Nevertheless, I agree with the authors: as antidepressants are so frequently prescribed, there is a need for further studies of antidepressant medications with regard to cardiac outcomes. A large registry study of a database of patients who were prescribed antidepressant medication, have known risk factors for CHD, and in whom cardiac outcomes are recorded over time may help address this important issue.

Lorraine Dennerstein AO, MBBS, PhD,
DPM, FRANZCP
Professorial Fellow
The University of Melbourne
Department of Psychiatry
National Ageing Research Institute
Melbourne, Australia

Reference:

Berkman LF, Blumenthal J, Burg M, et al, for the ENRICH investigators. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICH) randomized trial. *JAMA* 2003;289:3106-3116.

Resting heart rate as predictor of coronary events

Hsia J, Larson JC, Ockene JK, et al, for the Women's Health Initiative Research Group. Resting heart rate as a low tech predictor of coronary events in women: prospective cohort study. *BMJ* 2009 Feb 3 [Epub ahead of print]. **Level of evidence: II-2.**

Abstract copyright © 2009 BMJ Publishing Group. All rights reserved. Used with permission.

OBJECTIVE: To evaluate resting heart rate as an independent predictor of cardiovascular risk in women. **DESIGN:** Prospective cohort study. **SETTING:** The Women's Health Initiative was undertaken at 40 research clinics in the United States. **PARTICIPANTS:** 129 135 postmenopausal women. **MAIN OUTCOME MEASURE:** Clinical cardiovascular events. **RESULTS:** During a mean of 7.8 (SD 1.6) years of follow up, 2281 women were identified with myocardial infarction or coronary death and 1877 with stroke. We evaluated associations between resting heart rate and cardiovascular events in Cox regression models adjusted for multiple covariates. Higher resting heart rate was independently associated with coronary events (hazard ratio 1.26, 95% confidence interval 1.11 to 1.42 for highest [>76 beats per minute] v lowest quintile [≤ 62 beats per minute]; $P=0.001$), but not with stroke. The relation between heart rate and coronary events did not differ between white women and women from other ethnic groups (P for interaction= 0.45) or between women with and without diabetes (P for interaction= 0.31), but it was stronger in women aged 50-64 at baseline than in those aged 65-79 (P for interaction= 0.009). **CONCLUSION:** Resting heart rate, a low tech and inexpensive measure of autonomic tone, independently predicts myocardial infarction or coronary death, but not stroke, in women.

Comment. I read this study by Hsia et al with great interest. My first thought: The Women's Health Initiative continues to be a treasure chest of information. My second thought: Does this article really add anything to my diagnostic acumen? It appears that resting heart rate does correlate with sympathetic tone and cardiovascular risk. However, elevated cholesterols, triglycerides, blood pressure, and body mass index certainly would have clued me in to risk prior to an elevated heart rate.

Hsia et al raise the importance of awareness of cardiovascular risk and prevention in

postmenopausal women, but more useful would be to see the same study done in high-risk women with a focus on movement, anti-inflammatory diet (elimination of sugar, especially fructose sugar, and trans fats), the addition of fish oil to the diet (which can decrease blood viscosity), and vitamin D. Teaching women to track resting heart rate would be an easy tool to encourage patients and to follow their results.

Now that would be a great study.

Kathryn Havens, MD, NCMP
 Director of Women's Health
 Veterans Administration
 Clement J. Zablocki VA Medical Center
 Milwaukee, WI
 NAMS Certified Menopause Practitioner

Editor's picks from May-June *Menopause*

NAMS spotlights the most recent issue of the Society's official journal, *Menopause*, selected by its Editor-in-Chief, Dr. Isaac Schiff.

Avis NE, Brockwell S, Randolph JF, Shen S, Cain VS, Ory M, Greendale GA. Longitudinal changes in sexual functioning as women transition through menopause: results from the Study of Women's Health Across the Nation. *Menopause* 2009;16:442-452.

Results showed that pain during sexual intercourse increased and sexual desire decreased over the transition, whereas masturbation increased during the early transition, but then declined in postmenopause.

◆
 Col N, Politi M, Guthrie J. Duration of vasomotor symptoms in middle-aged women: a longitudinal study. *Menopause* 2009;16:453-457.

Primary data from 438 women in a 13-year longitudinal cohort study were reanalyzed to estimate the duration of vasomotor hot flashes. The average duration of vasomotor symptoms in this sample is more than 5 years, substantially longer than previously reported.

◆
Grady D, Sawaya GF, Johnson KC, et al. MF101, a selective estrogen receptor β modulator for the treatment of menopausal hot flashes: a phase II clinical trial. *Menopause* 2009;16:458-465.

Results of a randomized, blinded, phase 2 trial in 217 postmenopausal women with hot flashes suggest that an estrogen-receptor β -selective Chinese herbal extract reduces the frequency of hot flashes.

◆
Wood CE, Lees CJ, Cline JM. Mammary gland and endometrial effects of testosterone in combination with oral estradiol and progesterone. *Menopause* 2009;16:466-476.

The findings of this study do not support the idea that testosterone antagonizes the effects of combined hormone therapy on breast proliferation or markers of estrogen-receptor

activity. Overall, the short-term effects of testosterone co-therapy on the mammary gland and endometrium were minimal.

◆
Bardia A, Novotny P, Sloan J, Barton D, Loprinzi C. Efficacy of nonestrogenic hot flash therapies among women stratified by breast cancer history and tamoxifen use: a pooled analysis. *Menopause* 2009;16:477-483.

A meta-analysis of available studies evaluated the use of nonestrogenic therapies for hot flashes in groups of participants with and without a history of breast cancer and in participants with and without the concurrent use of tamoxifen, supporting that these treatments affect hot flashes equally well in all of these participant groups.

The level of evidence indicated for each study is based on a grading system that evaluates the scientific rigor of the study design, as developed by the US Preventive Services Task Force. A synopsis of the levels is presented below.

Level I	Properly randomized, controlled trial.
Level II-1	Well-designed controlled trial but without randomization.
Level II-2	Well-designed cohort or case-control analytic study.
Level II-3	Multiple time series with or without the intervention (eg, cross-sectional and uncontrolled investigational studies).
Level III	Meta-analyses; reports from expert committees; descriptive studies and case reports.

Need to refer patients to the NAMS Web site?

You know that The North American Menopause Society (NAMS) Web site is an outstanding educational resource for you and your patients. How can you best convey the message to your patients? NAMS produces handy cards you can order for distribution in your office so all will be aware of how the NAMS Web site can help.

Bundles of 100 Web Site InfoCards are available at a very low cost (\$30 members; \$40 nonmembers); the cost includes shipping to US locations. The cards can be ordered online at the NAMS Web site (www.menopause.org).

First to Know[®] is a registered trademark of The North American Menopause Society

Copyright © 2009 The North American Menopause Society
All rights reserved
5900 Landerbrook Drive, Suite 390
Mayfield Heights, OH 44124, USA
Tel 440/442-7550 • Fax 440/442-2660 • info@menopause.org
www.menopause.org